Medication safety in patients with cirrhosis

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Chapter 5

General discussion

Parts of this discussion have been submitted

Patients with cirrhosis have a high risk of adverse drug reactions (ADRs). These patients need tailored pharmacotherapy to avoid ADRs. In this thesis, we developed practical guidance for healthcare professionals. In addition, the current practice of prescribing by physicians and safety monitoring by community pharmacists was explored to identify areas of improvement for safe medication use in patients with cirrhosis. At last, the quality of data from pre- and post-marketing information sources on safe medication use in patients with cirrhosis was studied.

Main findings from this thesis

Chapter 2 of this thesis described the development of practical guidance. In the first part, the method used to evaluate the safety and dosing of medication in patients with cirrhosis was provided (Chapter 2.1). Using this method, recommendations for over 200 medicines were formulated (Chapter 2.4). Nearly 70 medicines were classified as unsafe in (a stage of) cirrhosis because of pharmacodynamic changes or large increases in exposure. Proton pump inhibitors (PPIs) are an example of medicines largely cleared by the liver. We showed in Chapter 2.2 that some PPIs are subjected to major pharmacokinetic changes in patients with cirrhosis and need to be avoided in the vulnerable, cirrhotic patient. Another example are the statins; in Chapter 2.3 we discussed the safety of simvastatin based on a recent trial that found a high incidence of a specific ADR (rhabdomyolysis) in patients with advanced cirrhosis. These chapters clearly demonstrated the importance of tailored pharmacotherapy in these patients, and provide safety and dose recommendations for medication frequently used in cirrhotic patients.

In Chapter 3, current practices in Dutch healthcare were explored. In a large, real-world cohort of patients with cirrhosis we showed that almost 40% of patients used a drug of which the safety was never clinically studied ("unknown"). Furthermore, 60% of patients used a potentially unsafe medicine: e.g., nonsteroidal anti-inflammatory drugs (NSAIDs) were frequently prescribed (Chapter 3.1). In Chapter 3.2, it was noticed that the level of knowledge among community pharmacists on medication safety in patients with cirrhosis was low. The pharmacists also experienced limited access to relevant patient data (e.g., diagnosis and severity of hepatic impairment) which may adversely affect their practice. Both chapters demonstrated areas for improving the current practice and consequently medication safety in patients with cirrhosis.

In Chapter 4 of this thesis, we assessed the quality of pre- and post-marketing information on safe drug use in cirrhosis. In Chapter 4.1, we showed that the Summaries of Product

Characteristics (SmPCs) of recently approved medicines contained a substantial part of information requested by the European Medicines Agency (EMA) on patients with hepatic impairment. Although available, the safety advice was often ambiguously formulated and therefore not clinically applicable. We also examined the quality of documentation of spontaneous ADR reports from the Lareb Pharmacovigilance Center (Chapter 4.2). We noticed that the documentation of the disease was often insufficient and that a specification of the severity of cirrhosis was lacking in most reports. The quality of information from these pre- and post-marketing information sources is therefore poor due to the lack of key patient data.

In this last Chapter, the results of this thesis will be put into a broader perspective. Three main topics emerging from this thesis will be discussed:

I. The term hepatic impairment in relation to medication
II. The pharmacology of adverse drug reactions in cirrhosis
III. The ways to optimize safe medication use in cirrhosis in practice

In each of the following sections, one topic will be discussed and implications for practice and further research will be provided. In the end, conclusions from this thesis are given and the most important implications for practice and further research.

The term hepatic impairment in relation to medication

An aspect that was noted in several of our studies was an ambiguous description of the patient population. In the SmPCs, recommendations on medication use were often provided for the undefined group of "patients with hepatic impairment". In addition, the severity of hepatic impairment was not always clearly described in data from pre- and post-marketing information sources.

Difficulties in defining hepatic impairment

The term hepatic impairment is ambiguous because there is no generally accepted definition [1]. This lack of a definition is probably due to the complexity of the topic. There is not a single (laboratory) parameter that assesses the remaining hepatic capacity to eliminate medicines [2, 3]. As a result, it is not easy to determine who suffers from an impaired hepatic function to eliminate medicines. The most commonly used classification for grading the severity of hepatic impairment (i.e. the Child-Pugh classification [4]) was not intended and validated for this purpose. The parameters it includes are not specific for hepatic function, and in case the Child-Pugh score is calculated in persons without cirrhosis they will all be categorized as "mild hepatic impairment", because that is the minimum score [5]. Hence, it cannot be used to determine if a patient suffers from hepatic impairment.

What we do know is that the liver functions are not easily affected by aging, nor by liver injury. There is evidence that the activity of hepatic enzymes declines with age, but because of the large overcapacity of the liver, this is not considered to alter the pharmacokinetics of medicines to a clinically relevant extent [6]. Hepatic impairment is therefore always the consequence of a hepatic disease [6]. Yet, a hepatic disease only affects the hepatic drug elimination function in an advanced stage [7]. The changes in pharmacokinetics that occur in patients with chronic liver diseases such as viral hepatitis or non-alcoholic fatty liver disease are usually minor compared to the changes seen in the advanced stage of the disease when cirrhosis is present [8-12]. This is also the current assumption in literature: mild changes in pharmacokinetics could occur in chronic liver disease, but only when the disease has progressed to cirrhosis, medication adjustments may be needed [2, 13]. The only exception could be cholestasis, for example caused by hepatic cancer or metastases, in which biliary excreted medicines can accumulate, however not much is known [2, 3]. Thus, a uniform definition of hepatic impairment is probably lacking due to the complexity of drug handling in the liver.

The clinical consequences of unclear information

Without a definition of hepatic impairment, misinterpretation could occur. Horak et al. [14] demonstrated the clinical consequences in their study with the anticancer drug gefitinib. They included healthy controls and two groups of patients with hepatic impairment, both with a different etiology. Patients with moderate hepatic impairment due to cirrhosis had twofold higher exposure to gefitinib as the healthy controls. Patients with moderate hepatic impairment due to cancer with hepatic metastases did not show this increase in exposure [14]. For the first group of patients, dose adjustments are probably needed to prevent ADRs, while dose adjustments could limit efficacy in the second group. Hence, providing medication advice on patients with hepatic impairment without defining this term can have serious consequences.

Clear information on the degree of hepatic impairment is also important. In the SmPC and in literature, two different classifications are frequently used: the Child-Pugh classification and the National Cancer Institute (NCI) criteria [4, 15]. Both use the same classes: mild, moderate and severe hepatic impairment. However, patients included in these classes have a different etiology of hepatic impairment. The Child-Pugh classification is designed and used in clinical practice as classification for the severity of cirrhosis [4]. The NCI criteria are, as the name suggests, used to classify the severity of hepatic impairment due to cancer (metastases) in the liver [16]. The study of Horak et al. on gefitinib compared both classification systems [14]. Half of the patients in their study with moderate and severe hepatic impairment according to the Child-Pugh classification, would have been classified as "normal hepatic function" using the NCI criteria [14]. This study confirms that it is of vital importance to explain both the etiology of hepatic impairment and the classification system used to grade the severity when describing patients in SmPCs or in literature.

Implications for practice and future research

As presented, the term "hepatic impairment" is ambiguous and can therefore be misleading. Hence, it would be better not to use the term "hepatic impairment" anymore in relation to medication in SmPCs, literature or other medication information sources. Instead, describe the etiology of the hepatic impairment (e.g., cirrhosis, hepatic metastases). This is a particularly important message for the EMA and the Food and Drug Administration (FDA). Both have guidelines for the pharmaceutical industry on how to evaluate the influence of hepatic impairment on the pharmacokinetics of new medicines [6, 17]. Yet, both guidelines do not specifically define hepatic impairment in terms of a hepatic disease. This is probably an important reason for the continuous use of the ambiguous term "hepatic impairment" in SmPCs and literature. Therefore, we urge the EMA and FDA to change their guideline on this point. In our practical guidance, we decided to focus on patients with cirrhosis because current literature suggests these patients are most at risk for alterations in pharmacokinetics [2, 13]. In addition, cirrhosis is a clearly defined disease stage [18]. Possibly, the EMA and FDA could follow our example.

With regard to grading the severity of hepatic impairment, the Child-Pugh classification is not an ideal classification system. It was not developed to grade the remaining capacity of the liver to eliminate medicines and it cannot be easily determined because it includes two parameters that are clinically graded by the gastroenterologist (i.e., the severity of ascites and the severity of hepatic encephalopathy) [5]. In further research, alternatives for the Child-Pugh classification should be explored. Due to the complexity of drug handling in the liver it can be questioned if there will ever be a simple parameter like creatinine clearance used in renal impairment. Another scoring system frequently used in these patients is the Model for End stage Liver Disease (MELD) score. This includes only laboratory parameters (i.e., bilirubin, creatinine and INR) [5]. A study showed that both the MELD-score and the Child-Pugh classification correlate with midazolam clearance [19]. A recent editorial described that the FDA is revising their guideline and might advise the use of the MELD-score [20]. If this is the case, it is highly recommended that it will include some sort of conversion table with the Child-Pugh classification, if possible, to avoid wasting all previous research and recommendations based on the Child-Pugh score.

Pharmacology of adverse drug reactions in cirrhosis

Patients with cirrhosis have a high risk of ADRs when using medicines because of alterations in the pharmacology of medicines (i.e., the pharmacokinetics (PK) or pharmacodynamics (PD)). To avoid medication harm, we classified 31% of 218 medicines as unsafe in (a stage of) cirrhosis and for 30% of medicines a dose adjustment was advised (Chapter 2.4). Surprisingly, a large part of medicines was classified as unsafe due to an increased risk of a specific ADR. Previous studies mostly focused on PK alterations occurring in cirrhosis and covered changes in the profile and frequency of ADRs in patients with cirrhosis only to a limited extent [2, 3, 13]. Therefore, we will go more into depth about the pharmacology of ADRs in patients with cirrhosis. This may help to better understand and recognize medication harm in patients with cirrhosis.

Croxen and colleagues probably made the most comprehensive overview of undesirable side effects in patients with liver disease [21]. By using the same classification of effects, Figure 1 was designed. This figure provides an overview of ADRs that patients with cirrhosis seem to be more susceptible to compared to healthy controls. It was composed based on (some of) the studies retrieved during the development of practical guidance. In addition, an explanation (i.e. the biological plausibility) for the increased sensitivity is given in the form of pathophysiological changes.

Renal effects

Probably most familiar are the harmful effects that medicines could have on kidney function in cirrhosis [22]. Several studies with NSAIDs [23-25] and a meta-analysis on renin-angiotensin-aldosterone system (RAAS) inhibitors [26] showed a high risk of renal impairment in patients with (advanced) cirrhosis. This is due to the alteration in systemic hemodynamics occurring in cirrhosis. Portal hypertension causes splanchnic vasodilation. To preserve renal function, the RAAS system is activated leading to excretion of renal vasodilators for the afferent arterioles (e.g., prostaglandins) and vasoconstrictors for the efferent arterioles (e.g., angiotensin-II (AT-II)) [27]. Medicines that interfere with this mechanism, such as RAAS-inhibitors and NSAIDs by inhibiting AT-II and prostaglandin synthesis respectively, could cause acute renal impairment [22].

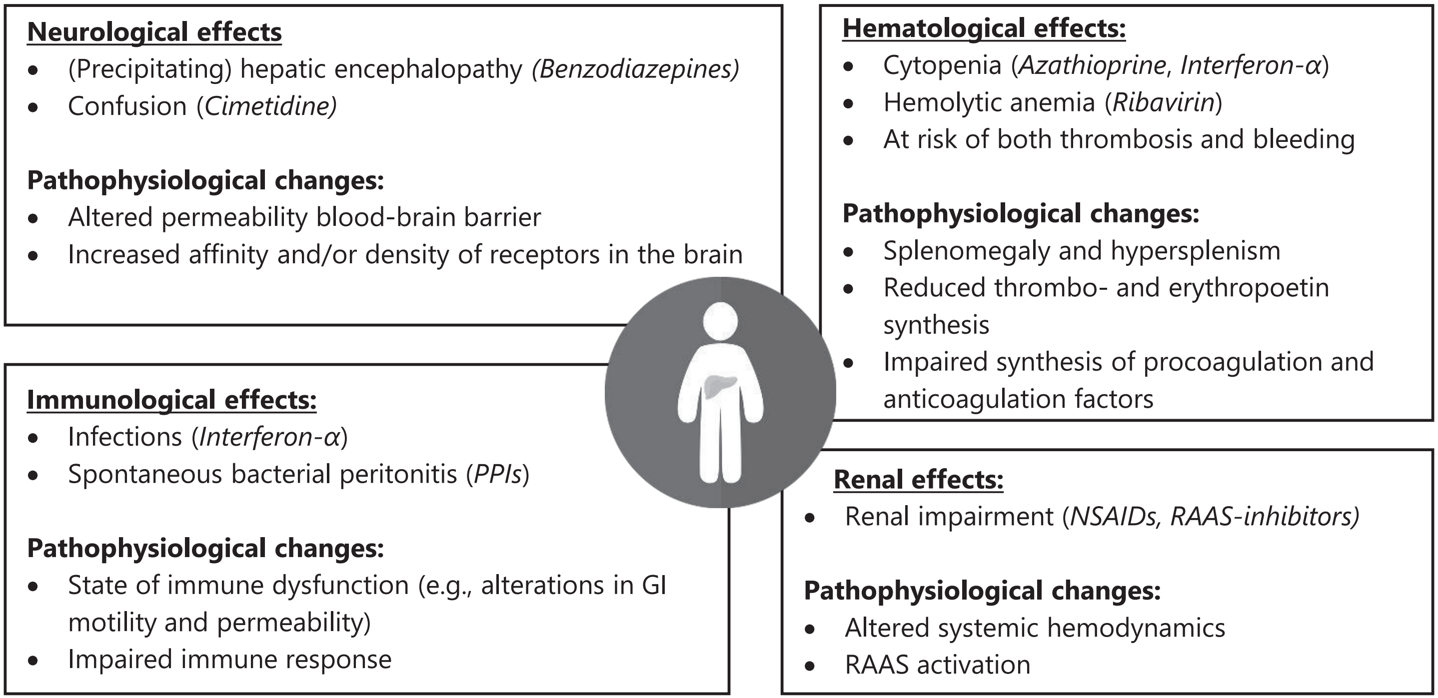

Figure 1. Overview of ADRs that patients with cirrhosis seem to be more susceptible to compared to healthy controls and underlying pathophysiological changes.

ADR: adverse drug reaction, GI: gastro-intestinal, PPIs: proton pump inhibitors, NSAIDS: non-steroidal anti-inflammatory drugs, RAAS: renin-angiotensin-aldosterone system

Immunological effects

Patients with cirrhosis are in a state of immune dysfunction due to a number of factors (e.g., increased mucosal permeability of the gastro-intestinal tract, a reduced activity of hepatic reticuloendothelial cells) [28, 29]. Immunosuppressive therapy (such as interferon-α) may worsen this state. Indeed, a higher prevalence of infections have been noted in cirrhotic patients on interferon-α therapy compared to healthy controls [30, 31]. PPIs are another group of drugs that have been associated with an increased risk of infections, such as spontaneous bacterial peritonitis in patients with cirrhosis (Chapter 2.2). This is explained by the increase in the pH of gastric acid caused by PPIs which could lead to bacterial colonization, overgrowth and translocation [32].

Neurological effects

Another more familiar risk is the neurotoxicity of medicines (e.g., confusion, hepatic encephalopathy (HE)) in patients with cirrhosis. A recent work demonstrated the significant role of medicines in precipitating HE [33]. Among 2810 patients, 5% of the 913 HE episodes were related to benzodiazepines, 4% to opioids and 1% to hypnotics. Another study showed that patients with cirrhosis using benzodiazepines for 3 to 10 days had a fivefold higher risk of developing HE than patients not using benzodiazepines [34]. Currently, there are two pathophysiological mechanisms proposed as underlying to this increased neurotoxicity: (1) a higher permeability of the blood-brain barrier (BBB) and (2) an increased density or affinity of certain receptors in the brain.

Focusing on the BBB-theory: in a recent study, several drugs and metabolites were found in the cerebrospinal fluid (CSF) of 14 patients with HE that were not present in the CSF of controls [35]. In addition, a doubled CSF to serum ratio of cimetidine in patients with cirrhosis was observed [36]. Both results suggest accumulation of medicines in the brain. The reason for the increased BBB permeability is not well known. It has been suggested that it is caused by high exposure to bilirubin leading to down-regulated or occupied efflux pumps (i.e. P-glycoprotein and multi-drug-resistance protein (MRP)-1) [35].

With regard to the increased sensitivity theory, at comparable (unbound) plasma levels of benzodiazepines, excessive sedation was noted in cirrhotic patients compared to controls [37-39]. Benzodiazepine levels in the CSF were not higher than those in controls [40]. Another study demonstrated an increased density of one type of benzodiazepine receptor ("peripheral-type") in the brain of deceased patients with HE [41]. The upregulation is possibly caused by inflammation [43]. The receptor binds, among others, benzodiazepine-like drugs. Activation leads to synthesis of neurosteroids that can modulate the gamma-aminobutyric acid (GABA)-A receptor system and have been linked to the pathogenesis of HE [42].

Hematological effects

Due to their disease, patients with cirrhosis frequently already have alterations in baseline hematological parameters. Portal hypertension can lead to hypersplenism and a lower platelet count [43, 44]. In addition, the liver synthesizes several proteins, such as hematopoietic growth factors (thrombopoietin and erythropoietin) and coagulation factors (procoagulants and anticoagulants) [45, 46]. We first discuss effects on hematopoiesis, followed by effects on coagulation.

Several medicines (e.g., azathioprine, interferon-α, ribavirin) have been linked to an increased risk of hematotoxicity in patients with cirrhosis. Myelosuppression is a well-known ADR of azathioprine and two studies showed that cytopenia was more prevalent in patients with cirrhosis compared to patients without cirrhosis [47, 48]. Of note, azathioprine is also metabolized by the liver and pharmacokinetics could alter in cirrhosis [49]. Interferon-α could provoke mild bone marrow suppression and a higher prevalence of neutropenia and thrombocytopenia was found in patients with cirrhosis compared to patients without [50, 51]. In addition, decreases in platelets and leukocytes were more marked in the patients with cirrhosis [52]. An article revealed that particularly patients with cirrhosis lacked an appropriate compensatory increase in thrombopoietin in response to thrombocytopenia [53]. Lastly, ribavirin is known for inducing haemolytic anaemia and a study with ribavirin demonstrated that a lower baseline platelet count resulted in a significantly higher drop in haemoglobin levels [54]. Patients with cirrhosis had a significantly lower baseline platelet count and the authors therefore described that not per se the histological diagnosis of cirrhosis, but more its clinical expression puts them at risk for more severe ribavirin-induced haemolytic anaemia [54].

The effects of medicines on coagulation in cirrhosis are quite complex. The hemostatic balance in patients with cirrhosis is very fragile, partly due to impaired hepatic synthesis of pro- and anticoagulants [45]. Therefore, patients with cirrhosis are at risk for both bleeding and thrombotic events [45]. Anticoagulant therapy is further challenged by the large involvement of the liver in the pharmacokinetics of these medicines. In addition, regular laboratory parameters to monitor therapy (e.g., INR) are often increased at baseline due to the before mentioned changes. Overall, anticoagulation therapy is complex and challenging in patients with cirrhosis and much is still unknown [45].

In summary, these data demonstrate the impact of cirrhosis on the pharmacology of medicines. Discrimination between PK (alterations in plasma levels or distribution of medicines) and PD changes (increased sensitivity for the (side) effect of the medicine) is difficult and in the described studies not always possible. The provided overview of ADRs is probably incomplete since some effects are still undetected or hardly studied. Detecting additional medication harm in patients with cirrhosis is quite challenging. We continue by discussing these challenges and the implications for practice and further research.

Implications for practice and future research

Patients with cirrhosis should receive pharmacotherapy tailored to the alterations in pharmacology. Healthcare professionals can be supported by the practical guidance for over 200 medications we developed (Chapter 2.4). However, there is no guidance for all medicines and for some, no concrete advice could be given due to limited or lacking clinical data.

There is a long list of remaining medicines of which the safety and optimal dose in cirrhosis is yet to be determined. The medicines on this list could be prioritized based on their use in patients with cirrhosis (Chapter 3.1). Another approach is to prioritize them based on expected harm. Medicines known to cause one of the before mentioned effects in healthy controls could be given priority, even as medicines largely cleared by the liver. For example: valproate, known to cause encephalopathy [55]; aminoglycosides, known to induce renal impairment [56]; or loperamide, subjected to a very large first-pass effect (F = 0.3%) [57]. A con of this approach is that unknown harms may be even more dangerous. Moreover, it is difficult to prioritize between sorts of harms, so prioritizing based on usage is probably a more judicious choice.

For clinical practice, precaution is needed when prescribing medicines with no advice, especially in patients with severe cirrhosis (Child-Pugh C), since they are most at risk for changes in pharmacology. The principle “start low, go slow” should certainly be followed in these situations. The patient should be closely monitored for signs of toxicity, with a particular focus on the effects discussed in the previous section. If an ADR occurs, one should try to assess if this is due to a too high dose for this patient or because of an increased susceptibility for this ADR. Especially in case of PK alterations, dose adjustments could be of help, while in case of an increased susceptibility, a lower dose could result in decreased efficacy. If an ADR is likely, it would be of great help to report it to the local pharmacovigilance center or publish it as a case-report to supplement knowledge in this area.

Challenges in studying medication safety in cirrhosis

There are still major gaps in knowledge on the safety and optimal dose of certain medicines in patients with cirrhosis. Therefore, more research is needed on both PK and PD alterations. The primary information about alterations in pharmacology in patients with cirrhosis originates from the pre-marketing studies conducted by the pharmaceutical industry. These studies concentrate on PK, as is also the focus of the EMA and FDA guideline [6, 17]. Both guidelines do acknowledge that PD can be changed in hepatic impairment and advise to include efficacy and safety endpoints in the PK studies when possible [6, 17]. Yet, this is limited by their design: a small number of patients (usually around six per severity class and often no patients with severe cirrhosis) and only a single dose of the study drug is administered. ADRs could be hard to detect because of a low frequency or because they resemble the natural course of cirrhosis [58]. As a result, it is likely that alterations in ADRs are not yet revealed during these pre-marketing studies. Larger studies with a longer follow-up are needed, which are usually performed in the post-marketing setting.

In this post-marketing phase, experimental research is wanted (e.g., PK studies, randomized controlled trials). However, performing these studies is complicated by difficulties in recruiting enough relative healthy cirrhosis subjects and by ethical concerns of research in such a patient group (especially in Child-Pugh C patients) [2]. As such, post-marketing information mostly results from clinical practice (e.g. spontaneous reporting, case-reports and case-series) and observational research. In particular for these types of research, a few methodological issues are important to consider.

In the first place, when evaluating additional medication harm in patients with cirrhosis, two questions are specifically relevant:

1. Is the harm an ADR or a complication of cirrhosis?
2. Is the harm more common in patients with cirrhosis than in healthy controls?

To best answer these question, a control group of patients with cirrhosis and one of healthy controls is desired. This approach was used in a study that assessed the risk of renal impairment by tobramycin in patients with liver dysfunction [59]. They wanted to control for both the effect of the drug (tobramycin) and the disease (liver dysfunction) itself on the adverse outcome of interest (renal impairment) [58, 59]. The authors used data from a randomized controlled trial, formed four groups (Table 1) and analyzed the results by multiple logistic regression with an interaction term. Liver disease alone did not significantly increase the odds of renal impairment. Tobramycin use did: the odds for developing renal dysfunction in healthy users was 6.0 [confidence interval (CI) 3.8-9.50]. Patients with liver dysfunction that used tobramycin had a relative odds of 31.8 [CI 19.7-51.4] for renal dysfunction. This study thoroughly demonstrated this drug-disease interaction and the design could be an example for further studies.

Table 1. Design to study renal impairment caused by tobramycin (n=179), as used by Moore et al [59].

<table>
<tr><th></th><th>Tobramycin (n=91)
(Drug of interest)</th><th>Cefotaxime (n=84)
(Comparable drug)</th><th></th></tr>
<tr><td>Liver dysfunction (n=29)</td><td>Group 1: renal impairment in 11/15 patients (73%)</td><td>Group 2: renal impairment in 0/14 patients (0%)</td><td rowspan="2">Effect of drug
Tobramycin: 37/91 (41%)
Cefotaxim: 7/84 (8%)</td></tr>
<tr><td>Controls (n=150)</td><td>Group 3: renal impairment in 26/76 patients (34%)</td><td>Group 4: renal impairment in 7/74 patients (9%)</td></tr>
<tr><td></td><td colspan="2">Effect of disease:
Liver dysfunction: 11/29 (38%)
Controls: 33/150 (22%)</td><td>Drug-disease interaction</td></tr>
</table>

In the second place, in research it is also important to discriminate between medication harm due to an overdose or due to an increased susceptibility. For example, in a study among patients with severe hepatic dysfunction, 23% of 39 patients that used β-lactam antibiotics developed leukopenia, compared to none of the 16 patients using other antibiotics [60]. The authors reported that this high frequency of leukopenia was probably caused by excessive serum concentrations, although these were not measured. Furthermore, they proposed dose reductions for β-lactam antibiotics in these patients. As previously elaborated, patients with cirrhosis can be more susceptible for hematotoxicity. As efficacy is important for antibiotics, dose adjustment should only be advised when PK data (i.e. (unbound) plasma levels) are available. PK changes are also sometimes overlooked in studies on the safety of medicines in patients with cirrhosis. We noted in our review of PPIs (Chapter 2.2) that almost all included safety studies determined the ADR risk and the dose-dependency of this risk for the complete group of PPIs. The PK of all PPIs change in cirrhosis, but for every PPI to a different extent. This can influence the ADR risk, which was confirmed in an article that demonstrated different odds for developing HE per PPI when these were stratified by individual PPI [61]. Therefore, try to also assess the ADR risk per individual medicine instead of only assessing the risk (or worse: the dose-dependency of the risk) for the complete medicine group.

Predicting (un)safe medication use

In situations where there is paucity of data, prediction or modelling studies could be of help. In particular for patients that are not likely to be included in (future) studies (i.e. patients with Child-Pugh C cirrhosis). A recent work used 84 published PK studies and combined the results with the individual drug PK parameters to assess if certain PK parameters correlated to larger PK alterations [62]. In patients with Child-Pugh B and C cirrhosis, a trend was found towards higher exposure to medicines with higher hepatic extraction ratios. However, the clinical meaning of this finding is uncertain since some medicines with a low hepatic extraction ratio also exhibited major increases in exposure. In addition, the only significant negative predictor for large PK alterations was extensive renal elimination [62]. If more than 40% of a medicine was excreted unchanged in urine, the increase in exposure was predicted to be less than twofold. Yet, this finding should be interpreted with caution since patients with severe cirrhosis also frequently suffer from (covert) renal impairment. Furthermore, it seems like the authors did not take the administration route of the study drugs into account in their analysis, which certainly influences PK changes in cirrhosis [63]. Despite these limitations, the interesting approach used in this study could be further explored. For example, by using all the PK data gained during our development of practical guidance. Alternatively, by an even larger method: an in-depth analysis of both the classification and dosing of medicines in our guidance. In this way, one could determine if certain drug characteristics (PK or PD parameters) correlate to an unsafe classification or a dose modification and use this knowledge to predict safety concerns or dose adjustments for other medicines.

Another way of predicting medication safety in patients with cirrhosis is using Big Data approaches based on real-world data. If patients with cirrhosis need essential treatment, they will be treated although (safety) evidence may be limited. The outcome of such pharmacotherapy can be valuable information for subsequent treatments. A work applied such a design to support clinical decision-making in geriatric oncology patients [64]. By using a large database of former patients with their characteristics and the results of their treatment, clinicians wanting to start treatment in new patients were supported with safety and efficacy outcome data on previous patients. In this manner, evidence level was shifted from expert opinion (level 5) to case-series (level 4) [64]. To use this approach in patients with cirrhosis, a large database would be needed because cirrhosis is not as common as cancer. This resembles a register design in which all patients with cirrhosis treated with a certain medicine are included to study safety outcomes of the treatment. This is a very interesting design, yet also challenging to perform and expensive.

The ways to optimize safe medication use in patients with cirrhosis

A recent Australian study showed that patients with decompensated cirrhosis suffered from a median of 6 medication-related problems per patient (range 2-17) [65]. Almost half of these problems was judged as high risk of potential harm to the patient. Besides inappropriate prescribing (incorrect choice of medicine or dosage), there were also several other medication-related problems noted (e.g., non-adherence, monitoring issues) [65]. This study demonstrated that improving medication safety in patients with cirrhosis is much broader than only the availability of practical guidance. In Figure 2, an overview is given of issues revealed in this thesis and in literature that currently limit optimal use of medicines in patients with cirrhosis and their risk factors. We start by discussing patient-related issues, then broaden our view to the healthcare professionals and subsequently to the information sources that healthcare professionals use for clinical decision-making.

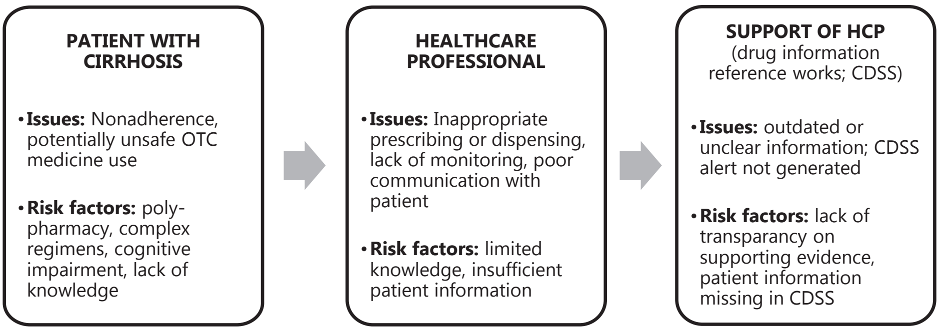

Figure 2. Issues that currently limit optimal use of medication in patients with cirrhosis and their risk factors.

CDSS, clinical decision support system; OTC, over-the-counter; HCP, healthcare professionals.

Patients

Nonadherence was the most common drug-related problem noted in patients with decompensated cirrhosis and can be either unintentional or intentional [65]. Risk factors for unintentional nonadherence in patients with cirrhosis could be the relatively large number of medicines used, the complex medication regimen and cognitive impairment [66-68]. Studies showed that patients with cirrhosis use a median of 5-10 different medicines per patient [65, 68, 69]. In addition, the medicines are often prescribed in a complex regimen. For example, lactulose needs to be titrated by the patient according to the number of bowel movements per day [66, 68]. Cirrhotic patients also frequently suffer from cognitive impairment as complication of their disease [68]. All these factors could lead to unintentional nonadherence. Adherence can also be intentional, for example due to the patients' perception of his disease and the necessity of treatment [65]. This could be prompted by a lack of knowledge about cirrhosis and the treatment among patients, which was demonstrated in two studies [70, 71].

A lack of knowledge among patients can also lead to another medication-related problem: the use of potentially unsafe over-the-counter (OTC) medicines, such as NSAIDs. The two studies that assessed knowledge level of patients also asked patients a question on the safety of OTC-medications [70, 71]. In both studies, more than half of the patients did not know that NSAIDs should be avoided [70, 71]. These data demonstrate that patients could use support in medication management and education on the disease and treatment.

Healthcare professionals

Optimal use of medicines in patients with cirrhosis can be limited by the healthcare professional through inappropriate prescribing or dispensing of medicines, a lack of monitoring, or poor communication with the patient. As demonstrated in Chapter 3.1, use of potentially unsafe medication was quite common among patients with cirrhosis. Yet, medication considered safe to use in cirrhosis, could also lead to ADRs and therefore the patients should always be monitored for signs of overdosing. Issues with monitoring led to medication-related problems in more than half of patients with cirrhosis in the Australian study [65]. Finally, poor communication with the patient could induce problems such as nonadherence. In two qualitative studies, some patients with cirrhosis suggested that their healthcare professionals did not inform them well enough about the disease and treatment which affected their self-management [72, 73].

These three issues could be caused by several factors, of which we discuss two important ones related to these specific patients. Namely, a limited knowledge on the topic and a lack of patient data among healthcare professionals. In Chapter 3.2, we showed that knowledge on medication safety in cirrhosis was limited among community pharmacists. Other research suggests that this lack of knowledge is also present among physicians, in particular those not specialized in gastroenterology [74-76]. The lack of patient information refers to information on the medicines the patients use and on the diagnosis and severity of cirrhosis. Literature showed that OTC medicines and complementary medicines were frequently lacking on the patients' medication list available to healthcare professionals [68, 77]. Yet, these medicines could interact with other medication or lead to ADRs, so it is important that healthcare professionals are aware of their use. The lack of data on the diagnosis and severity of cirrhosis was indicated by community pharmacists and general practitioners in Chapter 3.2 and consequences will be discussed in the following paragraph.

Support of healthcare professionals

In deciding on safe prescribing or dispensing of medicines in patients with cirrhosis, healthcare professionals are supported by information from drug information reference works. An example is the Pharmaceutical Compass, the major prescribing information source for physicians in the Netherlands [78]. An international example is Micromedex® [79]. Outdated or unclear advice in such reference works increases the risk of inappropriate prescribing and can subsequently lead to suboptimal medication use in patients with cirrhosis. The information provided in these reference works is largely based on the product information (i.e., the Summary of Product Characteristics (SmPC)) [80]. Yet, discrepancies have been observed between the advice in SmPCs and published literature on the safety of certain medicines in patients with hepatic impairment [1]. Furthermore, our research group and other groups noted key deficits and vagueness in the advice of SmPCs on patients with hepatic impairment (Chapter 4.1) [1, 80, 81]. It is difficult to determine the exact cause of such discrepancies or vagueness in advice because the SmPC is currently not very transparent about the supporting evidence [82].

To further support healthcare professionals in safe prescribing and dispensing, clinical decision support systems (CDSS) are frequently used that could alert the professionals for potentially unsafe drug use [82, 83]. However, an alert only appears if the patient is correctly marked in the CDSS [83]. If “cirrhosis” is not entered in the patient’s record, the medication safety alerts will not be generated and therefore be missed by the healthcare professional [83]. In Chapter 3.2, we demonstrated that both the diagnosis and severity of cirrhosis are often not known by community pharmacists, nor by some general practitioners. This currently limits the support of healthcare professionals by CDSS and therefore medication safety in patients with cirrhosis.

Implications for practice and future research

Support of healthcare professionals

The SmPC remains the primary source of information on medicines. Therefore, in an ideal situation, it should be up-to-date. To check if all relevant literature is included in the risk/benefit assessment for patients with cirrhosis, transparency about the supporting evidence is needed. For the European situation, the European Public Assessment Report (EPAR) is probably best suited for this background information. It is also described in literature that there is a desire for the EPAR to be a sort of living document, fitting in the bigger wish for more transparency at the EMA [84, 85].

To improve support of healthcare professionals by CDSS, exchange of key patient data (i.e. the diagnosis and severity of cirrhosis) between professionals should be encouraged. In the ideal situation, the gastroenterologist enters the diagnosis and severity of cirrhosis in the hospital CDSS and this is automatically exchanged between healthcare providers in primary and secondary care [83]. A more short-term approach is the organization of pharmacotherapy audit meetings between general practitioners and pharmacists on this topic to discuss practicalities limiting the exchange of the diagnosis and severity of cirrhosis.

Healthcare professionals

There is abundant room for improving medication safety and management in patients with cirrhosis by healthcare professionals. A relatively simple way is to improve the knowledge of healthcare professionals on medication safety in cirrhosis. During the pharmacy and medicine undergraduate studies, basic knowledge and awareness for this patient group could be created. In a postgraduate course, more advanced practice-based education could be provided.

A more demanding method to improve medication care in cirrhosis is establishing multidisciplinary cirrhosis care teams to enhance care coordination [66, 86]. In such teams, the patient's specific needs could be more easily aligned to the appropriate team member. The authors of one study proposed a very broad number of team members (e.g., hepatologists, mid-level care providers (nurse practitioners), pharmacists and specialists in certain areas such as palliative care and addiction) [86]. Another review article more aimed at medication proposed a smaller team consisting of physicians, nurses and pharmacists [66].

Pharmacists, as medication experts, could play an important role in terms of medication. They can assess adherence, support the patient with medication management and monitor the patient for possible signs of toxicity [87]. This was demonstrated in a recent trial where 375 medication related-problems were identified by a pharmacist and almost 60% was resolved by this pharmacist during a medication review [65]. An implication of this trial could be that pharmacists-led medication reviews in patients with cirrhosis should be implemented on a larger scale. Yet, there are some barriers to overcome. At least in the Netherlands, pharmacists need to be better trained in medication safety in cirrhosis because current knowledge level is low. Because of the complexity of the topic, one can also argue if it may be better to have a specialized (clinical) pharmacist in every region. Therefore, not every pharmacist needs to be familiar with the complete topic, but can consult a specialized pharmacist when in doubt about medication safety in a patient. Furthermore, other healthcare professionals (e.g., the general practitioner, gastroenterologist, nurses), could also consult this specialized pharmacist with medication-related questions. This could possibly save time for both the general practitioner and gastroenterologist, who could focus on diagnosing and treating the liver disease and co-morbidities. This results in the medication care team as depicted in Table 2. In a further study, the effect of such a care team on (patient-reported) outcomes (e.g., ADRs, adherence, and quality of life) could be determined.

Patients

In the proposed care team, pharmacists could support cirrhotic patients with their medication management, for instance by specific adherence tools (e.g., smart pill dispensers or package systems). The knowledge gap among the patients implies that they should be better informed about medicines and the additional risks in cirrhosis [70, 71, 88]. This could also be a task of the specialized pharmacists. More short-term approaches are as well possible. For example, development of a patient information leaflet on medication use in cirrhosis. Previous work revealed that an information leaflet on cirrhosis and self-management significantly improved knowledge among patients [70, 71]. On our website, we also included a part for patients with concise advice on the use of medicines in cirrhosis. A further study could assess if patients comply with the advice on our website and if not, what the reasons are for noncompliance.

Another group of persons to take into account are the caregivers of the patient. A study demonstrated that caregivers also feel responsible for medication management in their relatives with cirrhosis and HE [89]. Pharmacists could support the caregivers with this medication management and be a source of medication information for them.

Table 2. Proposed care team to improve safe medication use in patients with cirrhosis

Primary care	**Secondary/tertiary care**
General practitioner • Treatment of minor ailments and coordination of this care • Exchange of diagnosis and severity of cirrhosis	Gastroenterologist/hepatologist • (Coordination of) treatment of the liver disease • Determines diagnosis and severity of cirrhosis
Community pharmacist • Checking medication safety of new prescriptions • Consults specialized pharmacist if necessary	Specialized (clinical) pharmacist • Monitoring pharmacotherapy (adherence and ADRs) • Answering medication-related questions • Medication review

This model focusses on the Dutch healthcare setting. ADR: adverse drug reactions.

Conclusions

This thesis is the first to provide practical guidance for tailored pharmacotherapy in patients with cirrhosis based on a transparent method. We confirmed that tailored pharmacotherapy is important in patients with cirrhosis to avoid ADRs due to alterations in the pharmacology of medicines. Several potential improvements for safe medication use in current practice were provided. Finally, we noticed a poor description of key patient data in pre- and post-marketing information sources.

The findings of this thesis have a number of implications for practice, of which we distilled the most important ones:

- The term "hepatic impairment" should not be used anymore in relation to medication. Instead, describe the etiology of the impairment (e.g., cirrhosis).
- There are still major deficits in knowledge on the safety and optimal dosage of (certain) medicines in cirrhosis. Therefore, precaution is needed when using these medicines, especially in Child-Pugh C patients. The patient should be closely monitored for ADRs, with a particular focus on the effects we discussed.
- Several patient- and healthcare-related factors currently limit optimal medication use in patients with cirrhosis. Specialized pharmacists could be of support to both the patient and other healthcare professionals.

This thesis laid the groundwork for future research on medication safety in patients with cirrhosis. Essential topics for further research are:

- Alternative measurements for the Child-Pugh classification should be explored that grade the remaining capacity of the liver to eliminate medicines. Preferably a score only consisting of laboratory measurements.
- Research is needed on the pharmacology of ADRs in patients with cirrhosis. A distinction between higher plasma levels and an increased sensitivity is important in such studies. In severe cirrhosis, alternative methods to predict medication safety and dosing should be studied.

To conclude, this thesis aimed to improve medication safety in patients with cirrhosis. To further improve medication safety, close collaboration between all different stakeholders is required: from regulatory agencies and the pharmaceutical industry, to healthcare professionals and the patients with cirrhosis.

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